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Therapies in ankylosing spondylitis—from clinical trials to clinical practice

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Abstract

Until recently, the therapeutic options for patients suffering from active AS comprised NSAIDs and TNF inhibitor therapy. Although these are effective in a significant proportion of patients, not all patients respond and some are intolerant to these therapies. Therefore, there is a clear unmet treatment need in AS patients. This article reviews the evidence for targets currently being studied in AS. This includes the IL-12/23 inhibitor ustekinumab, the pan-Janus kinase inhibitor tofacitinib and the anti-IL-17A antibody secukinumab.

Key words: ankylosing spondylitis, management, therapy

Rheumatology key messages

- 20–40% of patients with AS do not respond to TNF inhibitor therapy.
- Secukinumab is the first IL-17A inhibitor approved for active AS.
- Both Janus kinases and IL-12/IL-23 inhibition show promise as targets in AS patients.

Introduction

AS is a chronic immune-mediated rheumatic disease that is characterized by inflammation and new bone formation predominantly in the axial skeleton [1].

Both NSAIDs and physical therapy should be considered in the treatment of AS [2]. Traditional DMARDs are ineffective in these patients [3].

TNF inhibitors (TNFis) have demonstrated improvements in the signs and symptoms of AS and in patient function [4–9], and are reserved for patients with persistently high disease activity (BASDAI >4; spinal visual analogue scale score >4) despite conventional treatments. For patients failing initial TNFi therapy, switching to a second TNFi or secukinumab is recommended [2, 10, 52].

Not all patients treated with a TNFi achieve acceptable clinical improvement during therapy. Indeed, ~20–40% of patients do not respond or are intolerant to these treatments and, among those that do respond, not all achieve remission [11]. In addition, patients who require TNFi therapy to be interrupted often experience disease relapse upon its reintroduction [12], and the effect of TNFis on new bone formation remains unclear [13–15], requiring further investigation. A recent study assessing the effects of TNFi on radiographic progression in 432 AS patients from the Swiss Clinical Quality Management cohort found that treatment with TNFis reduced the odds of progression [defined as an increase of $\geqslant 2$ U on the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) in 2 years] by 50% (odds ratio: 0.50, 95% CI: 0.28, 0.88) [16].

The introduction and success of TNFi treatment has raised the bar for treatment of AS, and hence increased the unmet clinical need for additional approaches to therapy in patients in whom TNFi therapy has failed or is contraindicated.

Over the past few years, various drug classes have been investigated for the treatment of patients with AS, the majority of which have failed to show significant efficacy. These include the IL-6 receptor inhibitors sarilumab and tocilizumab [17, 18], the T cell co-stimulation inhibitor abatacept [19], the IL-1 receptor antagonist anakinra [20], the phosphodiesterase-4 inhibitor apremilast [21, 22] and the anti-CD20 antibody rituximab [23].

This article reviews the evidence for targets currently being studied in AS. This includes the IL-12/23 inhibitor ustekinumab, the pan-Janus kinase (JAK) inhibitor tofacitinib and the anti-IL-17A antibody secukinumab.

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REVIEW

Targeting IL-12 and IL-23

The IL-23/Th17 axis is emerging as an important inflammatory pathway. Strong associations with the *IL23R* gene (encoding the IL-23 receptor) and polymorphisms within it have been shown in AS, suggesting that IL-23 may be involved in disease pathogenesis [24, 25].

Interestingly, protection from AS is conferred by an *IL23R* variant, due to reductions in responsiveness to IL-23 and downstream factors including IL-17 [26].

In terms of cytokine overexpression, elevated IL-23 levels have been reported in AS, and increased numbers of IL-23-responsive Th17 cells have been demonstrated among peripheral blood mononuclear cells from AS patients [27, 28].

The number of IL-12- and IL-23-positive cells in the bone marrow of facet joints from AS patients was significantly higher in comparison with samples obtained from patients with OA and from individuals without spinal disease [29].

Ustekinumab is a fully human mAb that binds to the p40 protein subunit of human IL-12 and IL-23. Two large phase 3 clinical trials (PSUMMIT-1 and PSUMMIT-2) showed the efficacy of ustekinumab in patients with active PsA, including those who had failed TNFi [30, 31]. In a *post hoc* analysis of data from these trials in a subset of patients with physician-identified spondylitis, significantly more patients treated with ustekinumab (54.8%) compared with placebo (32.9%) achieved a $\geqslant$20% improvement in BASDAI (BASDAI 20) at week 24 ($P \leqslant 0.001$) [32]. Ustekinumab-treated patients were also more likely than placebo-treated patients to achieve BASDAI 50 (29.3 *vs* 11.4%, respectively) and BASDAI 70 (15.3 *vs* 0%, respectively). Furthermore, at weeks 12 and 24, the ustekinumab group experienced significant improvements in Ankylosing Spondylitis DAS–CRP, with mean improvements approaching 30% at week 24 (compared with $<$5% in the placebo group).

In a recent prospective, open-label, single-arm, proof-of-concept study (Treatment of Patients With Active Ankylosing Spondylitis [TOPAS]), ustekinumab 90 mg was administered s.c. at baseline and at weeks 4 and 16 in 20 patients with active AS [33]. The proportion of subjects who achieved the primary endpoint—Assessment of SpondyloArthritis International Society (ASAS) 40 response at week 24—was 65%. Key secondary endpoints also showed clinically meaningful improvements: at week 24, 75% of subjects achieved ASAS 20 and 55% achieved a BASDAI 50 response. Ustekinumab was also associated with significant improvements in other patient-reported outcome parameters and in active inflammation as detected using MRI. Ustekinumab was well tolerated in this study and no new safety signals were detected [33]. Although this was a small, uncontrolled, open-label study, the efficacy and safety data were sufficiently promising to warrant further investigation.

Data from TOPAS prompted the initiation of a multicentre phase 3 trial programme. The first of two randomized phase 3 trials investigated the efficacy of ustekinumab compared with placebo in patients with AS, following an inadequate response or intolerance to TNFi therapy (TNFi-IR) [34, 35]. Patients received ustekinumab 45 or 90 mg s.c. at weeks 0 and 4, and then every 12 weeks to week 52. Patients in the placebo group received s.c. placebo injections at weeks 0, 4 and 16 before being re-randomized to ustekinumab 45 or 90 mg, with s.c. injections at weeks 24 and 28 and every 12 weeks thereafter [34]. The second phase 3 trial included patients with non-radiographic axial spondyloarthritis, and compared ustekinumab (45 or 90 mg) with placebo. Up to week 52, ustekinumab was administered according to the same schedule as that described for the phase 3 study in AS. Placebo was administered every 4 weeks until week 24, when patients were switched to ustekinumab [35]. These studies have been terminated since ustekinumab did not achieve key endpoints in a related study [34, 35].

Targeting JAK signalling

Evidence suggests that inhibition of JAK-mediated pathways may be a promising approach for the treatment of patients with chronic disease [36].

Activation of JAK pathways initiates the expression of survival factors, cytokines, chemokines and other molecules that facilitate leucocyte cellular trafficking and cell proliferation, contributing to inflammatory and autoimmune disorders. Hence, the JAK family has evoked considerable interest for the potential treatment of inflammatory diseases, leading to the development of various JAK inhibitors with different selectivity profiles against JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2.

Tofacitinib, for example, is a first-in-class pan-JAK inhibitor with potent inhibition of JAK3 and JAK1 and minor inhibition of JAK2. It interrupts the signal transduction of cytokines that contribute to the aberrant immune response in AS [37].

In a 16-week phase 2 study, $\sim$200 patients with active AS were randomized to receive one of three doses of tofacitinib (2, 5 or 10 mg), or placebo, twice daily for 12 weeks, with 4 weeks of follow-up [38]. Patients were assessed by MRI at baseline and after 12 weeks of treatment. A higher proportion of patients receiving tofacitinib 10 mg twice daily experienced an ASAS 20 response than those taking tofacitinib 5 or 2 mg or placebo (67.4, 63.0, 56.0 and 40.1%, respectively). Improvements in other clinical measures, including ASAS 40, Ankylosing Spondylitis DAS–CRP and BASDAI 50, were comparable for placebo and all tofacitinib doses. The 5 and 10 mg regimens resulted in significantly improved Spondyloarthritis Research Consortium of Canada sacroiliac joint and spine scores from baseline to week 12, compared with placebo. There were no new safety concerns reported for tofacitinib patients. Dose-dependent laboratory measures also appeared normal, resolving back to baseline values by week 16 of treatment.

Overall, tofacitinib 5 and 10 mg twice daily demonstrated greater clinical and imaging efficacy than placebo in reducing the signs and symptoms of disease in adults with active AS. Further studies are required to examine the efficacy of tofacitinib in active AS.

Targeting IL-17

Emerging evidence suggests that IL-17 plays a role as an inflammatory mediator in patients with AS. Elevated levels of serum IL-17 and an increased number of circulating Th17 cells have been detected in AS patients [27], and more IL-17-producing cells were detected in the facet joints of patients with AS compared with those with OA [29]. Animal data suggest that IL-17 blockade reduces RANK ligand-dependent osteoclastogenesis upstream of TNFα [39].

Secukinumab is a recombinant, fully human, monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype. In a double-blind, placebo-controlled, multicentre, proof-of-concept study of 30 patients with active AS, two doses of i.v. secukinumab 10 mg/kg (given 3 weeks apart) demonstrated substantial efficacy: the ASAS 20 response rate at week 6 was 59% in the secukinumab group compared with 24% for placebo [40]. Moreover, IL-17A blockade with secukinumab reduced spinal inflammation, as detected by MRI, in patients with AS as early as week 6 and sustained this effect up to week 28 [41].

The positive response of patients with active AS to IL-17A blockade with secukinumab observed in the proof-of-concept trial prompted the initiation of the MEASURE programme, which assessed the efficacy and safety of secukinumab in more than 1000 patients with active AS.

MEASURE 1 was a 2-year study with a 3-year extension phase enrolling patients with active AS [42]. It included both patients who were TNFi-naïve and TNFi-IR. Patients received a 10 mg/kg i.v. infusion of secukinumab at baseline and at weeks 2 and 4, followed by monthly s.c. doses, up to week 52, of either 75 or 150 mg. MEASURE 2 was a 5-year study that examined the use of secukinumab without an i.v. loading dose, with similar enrolment criteria to MEASURE 1 [42]. Patients received s.c. once weekly doses (either 75 or 150 mg) at baseline and at weeks 1, 2, 3 and 4, followed by monthly s.c. doses, up to week 52, of either 75 or 150 mg.

In MEASURE 1 (with i.v. loading), both secukinumab groups met the primary endpoint, with ASAS 20 response rates at week 16 of 61% with secukinumab 150 mg and 60% with secukinumab 75 mg, compared with 29% with placebo [40]. In MEASURE 2, only the 150 mg dose was significantly more efficacious than placebo, with an ASAS 20 response rate of 61%, compared with 41% with secukinumab 75 mg and 28% with placebo [42].

In MEASURE 1, all predefined secondary endpoints were met in both secukinumab groups: the ASAS 40 response rates at week 16 were 42, 33 and 13% in the secukinumab 150 and 75 mg and placebo groups, respectively. In MEASURE 2, all predefined secondary endpoints except ASAS partial remission were met with secukinumab 150 mg; based on hierarchical testing, responses with secukinumab 75 mg were not significantly different *vs* placebo. Week 16 responses were maintained at week 52 [42].

The effects of secukinumab on objective signs of inflammation in the sacroiliac joint and spine, as assessed by MRI, were evaluated in MEASURE 1. At week 16, improvements were seen in Berlin sacroiliac joint total oedema score, AS spine MRI score for activity and Berlin spine score with secukinumab *vs* placebo [43]. Spinal radiographic progression was also assessed in patients who received secukinumab at week 104 in MEASURE 1 using the mSASSS. Overall, the mean (S.D.) change in mSASSS from baseline to week 104 was small [0.3 (2.5)] [44] Although this change in mSASSS suggests a low mean progression of spinal radiographic damage, and the two independent X-ray readers were blinded to treatment (placebo or treatment arm) and radiograph sequence (baseline or week 104), a limitation of this analysis is the lack of comparator group beyond week 16. These data will need to be confirmed in a longer-term controlled study.

Clinical improvements in signs and symptoms with both doses of secukinumab in MEASURE 1 and with secukinumab 150 mg in MEASURE 2 were rapid and sustained through 52 weeks of treatment. These clinical benefits were observed both in TNFi-IR patients and in those who were TNFi-naïve [42, 45].

In the phase 3 MEASURE 3 study, patients were randomized to receive i.v. secukinumab 10 mg/kg at baseline and in weeks 2 and 4, followed by s.c. secukinumab 300 or 150 mg every 4 weeks thereafter, or to placebo [46]. At week 16, placebo patients were re-randomized to s.c. secukinumab 300 or 150 mg every 4 weeks. Approximately 77% of patients were anti-TNF-naïve.

The primary endpoint was met with both secukinumab regimens at week 16: the ASAS 20 response rate was 60.5% with secukinumab 300 mg and 58.1% with secukinumab 150 mg, *vs* 36.8% with placebo [6]. Improvements were seen as early as week 1. All secondary endpoints (ASAS 40, high-sensitivity CRP test, ASAS 5/6 and BASDAI) were met at week 16 with both dose regimens, except ASAS partial remission in the secukinumab 150 mg group. ASAS 20 and ASAS 40 response rates were higher with both secukinumab regimens *vs* placebo in both TNFi-naïve and TNFi-IR patients; response rates were higher in TNFi-naïve patients compared with those who were TNFi-IR.

The safety profile of secukinumab in AS is in accordance with that observed in psoriasis and PsA. Based on evidence from the secukinumab psoriasis clinical development programme, which included pooled data from 3430 patients across 10 phase 2 and 3 studies (amounting to 2725 patient-years of exposure), secukinumab has an acceptable safety profile that was comparable with those of etanercept and ustekinumab in 52 week studies [47–49].

In AS, there was a higher incidence of infections with secukinumab than with placebo, with pooled exposure-adjusted incidence rates of 0.7 events/100 patient-years for grade 3 or 4 neutropenia, 0.9 events/100 patient-years for *Candida* infections and 0.7 events/100 patient-years for Crohn's disease [42].

Two further phase 3 studies with secukinumab are ongoing: MEASURE 4 is investigating the efficacy of secukinumab every 4 weeks with or without an initial loading regimen and MEASURE 5 is investigating secukinumab in early, non-radiographic axial spondyloarthritis [50, 51].

Overall, the results from the MEASURE trials suggest that IL-17A plays an important role in the pathogenesis of AS and support the use of secukinumab as a treatment for these patients. The 150 mg s.c. dose appeared to be the most effective, and preliminary loading with i.v. secukinumab did not add any significant benefit. Although no head-to-head trials have yet been completed, and indirect comparisons should always be interpreted with caution, the efficacy achieved with secukinumab in AS appears comparable to that reported in phase 3 trials of TNFis in mostly biologic-naïve patients.

Conclusion

Over the past decade TNFis have revolutionized the management of AS. However, ~20–40% of patients do not respond or are intolerant to TNFis, and not all of those that do respond reach remission [11]. Hence, there remains a clear unmet need in AS. Large numbers of clinical trials have examined potential alternatives, with mixed results.

Secukinumab, at a dose of 150 mg every month with an initial loading phase in the first 4 weeks, is the first IL-17A inhibitor approved as a systemic treatment for active AS in adult patients with an inadequate response to conventional therapies such as NSAIDs. In the UK, it has received approval from the National Institute for Health and Care Excellence within its marketing authorization in adults whose disease has responded inadequately to conventional therapy (NSAID or TNFis) [52].

This licence is an important addition to the AS treatment armamentarium, being the first treatment approved in over a decade and offering the only alternative biologic therapy to TNFis in this indication.

It is hoped that the other agents discussed will also demonstrate efficacy and safety in phase 3 trials, resulting in additional approvals for this indication and further increasing the armamentarium of drugs for AS.

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